REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-60 are in this case. Claims 3-4, 16-28, 31-32 and 44-60 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-2, 5-15, 29-30 and 33-43 have been rejected. Claims 1-2, 5-15, 29-30 and 33-43 have now been canceled. New claims 61-74 have now been added.

35 U.S.C. § 112, Second Paragraph: Indefiniteness

The Examiner has rejected claims 1-2, 5-10, 29-30 and 33-39 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claims 1-2, 5-10, 29-30 and 33-43 have now been canceled, rendering moot the Examiner's rejection. Claims 61-74 have now been added.

In the interest of expediting prosecution in this case, Applicant has elected to reintroduce the subject matter of claims 1-2, 5-15, 29-30 and 33-43 in newly added claims 61-74. New claims 61-74 forgo the use of the terms on which the Examiner based the indefiniteness rejection and present the subject matter of the invention in a more concise and accurate manner thus greatly facilitating examination of this case.

35 U.S.C. § 102(b) Rejection - Vogelstein et al.

The Examiner has rejected claims 1-2, 5-15, 29-30 and 33-43 under 35 U.S.C. § 102(b) as being anticipated by Vogelstein et al. (W) 98/53319). The Examiner's rejections are respectfully traversed. Claims 1-2, 5-15, 29-30 and 33-43 have now been cancelled. New claims 61-74 have now been added.

The Examiner states that Vogelstein et al. teach an oligonucleotide library comprising a plurality of oligonucleotides, wherein each oligonucleotide is capable of specifically hybridizing to sets of messenger RNAs transcribed from a multiplicity of genes. The Examiner further states that Vogelstein et al. also teach that the

transcripts are derived from normal and pathological tissues of a human and that the oligonucleotide probes can be attached to an array.

As is stated throughout the instant application the present invention was devised in efforts of overcoming a severe limitation inherent to prior art probe libraries (e.g., Vogelstein et al.). Prior art probe libraries include oligonucleotide probes which are typically designed for identifying a single transcript produced from a transcription unit. Thus, prior art libraries cannot be utilized to accurately quantify the level of transcription and/or determine the quality of transcripts produced from a transcription unit or units under specific conditions or in specific tissues.

As is illustrated in the instant application the present inventors conducted laborious and time consuming experimentation in order to identify unique sequence regions which are shared by a set of mRNA splice variants produced from a transcription unit. Due to their unique design probes produced using such an approach enable accurate and rapid quantification and qualification of transcription from a specific transcription unit. As such, the present invention greatly enhances mRNA screening technology and can thus be used to more accurately assess gene expression and its implications in various tissues and conditions.

Although Vogelstein et al. describe an oligonucleotide library which can be utilized to identify transcript sets, the purpose of their oligonucleotide library and thus the nature of the oligonucleotide probes utilized negates identification of alternatively spliced variants transcribed from a single transcription unit and thus makes it impossible to accurately quantify the level of transcription and/or determine the quality of transcripts produced from a transcription unit.

In fact, since the oligonucleotide probes generated by Vogelstein et al. correspond to genes which are uniquely expressed in cancer tissue (see page 13, lines 3-9) as determined by transcript levels, no attempt was made to identify alternative transcripts nor was there incentive to do so.

Since the present invention as claimed is directed at a library which includes oligonucleotide probes each capable of selectively hybridizing to a set of RNA splice variants produced from one transcription unit, it is Applicant's strong opinion that Vogelstein et al. which do not suggest or describe design of such probes, or for that

matter target identification of splice variants, do not anticipate the invention claimed in New claims 61-74.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 102(b) rejections.

35 U.S.C. § 102(b) Rejections - Hardy et al.

The Examiner has rejected claims 1-2, 5, 8, 9, 29, 30, 34, 36 and 37 under 35 U.S.C. § 102(b) as being anticipated by Hardy et al. (EP 0791 660 A1). The Examiner's rejections are respectfully traversed. Claims 1-2, 5, 8, 9, 29, 30, 34, 36 and 37 have now been cancelled. New claims 61-74 have now been added.

The Examiner points out that Hardy et al. describe a library of oligonucleotides wherein each of the oligonucleotides is capable of hybridizing to one or a set or subset of mRNAs transcribed from a given transcription unit.

Contrary to the Examiner's assertion, Hardy et al. do not attempt to quantify expression from a given transcription unit or a collection of transcription units constituting a transcriptome or sub transcriptome but rather target identification of specific splice variants which arise from mutations and as such can be utilized as disease targets or markers. Hardy et al teach a method of identifying specific alternatively spliced isoforms which vary in sequence. Such isoforms may be used in diagnosing and treating neurodegenerative diseases. As such, the library generated by Hardy et al. represents the exact opposite of the library of the present invention in that the Hardy library attempts to identify specific splice variants of a transcription unit, whereas the library of the present invention attempts to identify some or all of the splice variants produced from a collection of transcription units. These differences in utility dictate radically different oligonucleotide design approaches which results in radically different probe sequences. In the oligonucleotide library described by Hardy et al. the probes are splice variant specific whereas in the oligonucleotide library of the present invention the probes are splice variant set specific.

Due to these profound differences in utility and thus probe design, it is Applicant's strong opinion that Hardy et al. do not anticipate the present invention as claimed.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 102(b) rejections.

35 U.S.C. § 102(a) and (e) Rejection - Lockhart et al.

The Examiner has rejected claims 1, 2, 5-15, 29,-30 and 33-43 under 35 U.S.C. § 102(a) and (e) as being anticipated by Lockhart et al. (US 6,040,138). The Examiner's rejections are respectfully traversed. Claims 1, 2, 5-15, 29,-30 and 33-43 have now been cancelled. New claims 61-74 have now been added.

The Examiner states that Lockhart et al. teach a library comprising a plurality of oligonucleotides capable of hybridizing with a set or subset of mRNAs transcribed from a multiplicity of genes of a genome.

As is argued hereinabove with respect to the 102(b) rejection the present invention specifically targets identification of all or some of the splice variants produced from each transcription unit of a transcriptome by utilizing a single oligonucleotide probe which is capable of hybridizing to several splice variants (set) generated by a single transcription unit.

In sharp contrast, the invention described by Lockhart et al. utilizes a high density array in which several probes each specific to a unique subsequence of the same gene are utilized in order to detect a single transcription unit (see column 9, lines 55-65). This approach is undertaken in order to traverse problems associated with cross reactivity, to identify closely related genes and to better normalize expression levels.

This prior art array design approach is radically different from that proposed by the present invention in which each probe can hybridize to several splice variants. Thus greatly simplifying array design.

It is therefore the Applicant's strong opinion that Lockhart et al. do not anticipate the present invention as claimed.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 102(a) (e) rejections.

35 U.S.C. § 102 (e) Rejection - Schweighoffer et al.

The Examiner has rejectcd claims 1, 2, 5-15, 29,-30 and 33-43 under 35 U.S.C. § 102(a) and (e) as being anticipated by Schweighoffer et al. (US 6,251,590 B1). Thc Examiner's rejections are respectfully traversed. Claims 1, 2, 5-15, 29,-30 and 33-43 have now been cancelled. New claims 61-74 have now been addcd.

The Examiner states that Schweighoffer et al. teach an oligonucleotide library comprising a plurality of oligonucleotides capable of hybridizing to alternative forms of splicing mRNAs typical of a pathological condition.

The library described by Schweighoffer et al. is somewhat similar to that described by Hardy et al. in that the oligonucleotide probes utilized by Schweighoffer et al. are not splice variant set specific but rather designed for the sole purpose of identifying splice variants which arc uniquely expressed in pathological tissue. In order to identify such splice variants, Schweighoffer et al. employ oligonucleotide probes which are capable of selectively hybridizing to one splice variant produced from transcription unit.

It is therefore the Applicant's strong opinion that Schweighoffer et al. do not anticipate the present invention as claimed.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 102(e) rejections.

35 U.S.C. § 102 (e) Rejection - Mack

The Examiner has rejected claims 1, 2, 5-15, 29,-30 and 33-43 under 35 U.S.C. § 102(a) and (e) as being anticipated by Mack (US 6,303,301 B1). The Examiner's rejections are respectfully traversed. Claims 1, 2, 5-15, 29,-30 and 33-43 have now been cancelled. New claims 61-74 have now been added.

The Examiner states that Mack teaches methods of identifying alternatively spliced variants. The Examiner further states that in columns 11-12 Mack discusses

alternative splicing and notes that in some embodiments of the present invention alternative splicing is monitored.

Applicant concedes that Mack indeed discusses alternative splicing, however monitoring of splice variants according to Mack is effected using an approach radically different from that of the present invention. As is clearly stated in column 12 lines 50-51 of US 6,303,301, in cases of alternative splicing "high density oligonucleotide arrays are particularly suitable" implying that splice variants of a single transcriptome can be detected if several probes, each unique to a single variant, are used. Further proof of this design approach is provided by the text of lines 53-55 of column 12 which states that oligonucleotide probes are synthesized in order to "detect the level of each of the sequences produced by alternative splicing and adenylation" again implying that Mack utilizes the one probe-one splice variant approach.

It is therefore the Applicant's strong opinion that Mack does not anticipate the present invention as claimed.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 102(e) rejections.

In view of the above amendments and remarks it is respectfully submitted that claims 61-74 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Registration No. 25,457

Date: September 7, 2003
Encl.
1-month extension fee